#15/A 9/26/02

Attorney Docket No. 13761-7001

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Dated: September 16, 2002

Name of Person Certifying: David Maher
Printed Name: David Maher

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Lenz, et al.	Assignee:	University of Southern California
Filing Date:	April 2, 2001	Examiner:	Unassigned
Serial No.:	09/824,629	Group Art Unit:	1634
Title:	MANGANESE SUPEROXIDE DISMUTASE GENE POLYMORPHISM FOR PREDICTING CANCER SUSCEPTIBILITY		

Commissioner for Patents
Washington, D.C. 20231

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.111

This is in response to the Office Action dated March 14, 2002 ("Office Action" or "Paper 12"). A three month extension of time is requested. Applicants respectfully request consideration of the above-identified application in view of the following amendments and remarks.

AMENDMENT

In The Claims

Please CANCEL claim 13, AMEND claims 14-28, and ADD claim 31 as follows. A clean copy of the pending claims under consideration is provided below. A marked up version of the amended claims is provided in Appendix I. Support for the claim amendments may be found throughout the application as originally filed, and in at least the following places: page 19 lines 4-25, page 3 line 23 through page 5 line 2, page 34 line 18 through page 37 line 7, Tables 1 and 2, and Figure 2. The claim amendments therefore add no new matter.

CLEAN COPY OF CLAIMS [PENDING AND UNDER CONSIDERATION]

A1

14. (Amended) The method of claim 21 comprising contacting a sample of the subject's nucleic acid comprising the MnSOD gene with a probe or primer which can hybridize to a region of the MnSOD gene encoding the MTS , said region including nucleotide 351 of SEQ ID NO:1.

15. (Amended) The method of claim 31, wherein determining whether an allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS comprises determining the identity of at least one nucleotide of the region encoding the MTS.

16. (Amended) The method of claim 31, wherein determining whether an allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS comprises performing a restriction enzyme site analysis.

17. (Amended) The method of claim 31, wherein determining whether an allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS comprises performing a single-stranded conformation polymorphism analysis.

18. (Amended) The method of claim 31, wherein determining whether an allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS comprises performing an allele specific hybridization.

19. (Amended) The method of claim 31, wherein determining whether an allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS comprises performing a primer specific extension.

20. (Amended) The method of claim 31, wherein determining whether an allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS comprises performing an oligonucleotide ligation assay.

21. (Amended) The method of claim 31, wherein the MnSOD gene is a human MnSOD gene.

22. (Amended) The method of claim 14, wherein the probe or primer has a nucleotide sequence from about 15 to about 30 nucleotides.

23. (Amended) The method of claim 31, wherein the probe or primer is labeled.

A1 cancel

24. (Amended) The method of claim 21, wherein determining whether an allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS comprises determining the base identity of a portion of genomic DNA from a sample from the subject, said genomic DNA comprising an MnSOD gene comprising a coding region for the mitochondrial targeting sequence, said portion corresponding to position 351 as defined in SEQ ID NO:1 of said MnSOD gene in said mitochondrial targeting sequence.

25. (Amended) The method of claim 24; wherein the base identity of said portion is determined by sequencing.

26. (Amended) The method of claim 24; wherein the base identity of said portion is determined by digesting said portion with an appropriate restriction endonuclease.

27. (Amended) The method of claim 24; wherein said base identity is determined by examining an RNA fraction from said subject's sample, whereby the identity of said genomic DNA at said position 351 can be determined.

both alleles →

28. (Amended) The method of claim 24; wherein the mutation in the coding region for the MTS resulting in a loss of α-helical structure in the MTS is a C at said position 351.

29. The method of claim 28; wherein the age of the subject is less than about 35 years.

30. The method of claim 29; wherein the ethnicity of the subject is Hispanic.

A2

--31. (New) A method of determining relative age-related risk of colorectal cancer in a subject susceptible thereto, comprising:

determining whether a first allele of a manganese superoxide dismutase (MnSOD) gene in the subject comprises a mutation in the coding region for the mitochondrial targeting sequence (MTS) of the MnSOD protein resulting in a loss of α-helical structure in the MTS;

determining whether a second allele of the MnSOD gene in the subject comprises a mutation in the coding region for the MTS of the MnSOD protein resulting in a loss of α-helical structure in the MTS;

assigning a lower risk of developing early onset colorectal cancer to a subject having no mutation in either the first or second allele of the MnSOD gene resulting in a loss of α-helical structure in the MTS;

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assigning a higher risk of developing early onset colorectal cancer to a subject having mutations in both the first and second alleles of the MnSOD gene resulting in a loss of α-helical structure in the MTS; and

assigning an intermediate risk of developing early onset colorectal cancer to a subject having a mutation in only one of the first and second allele of the MnSOD gene resulting in a loss of α-helical structure in the MTS.—

REMARKS

I. Rejections Under 35 U.S.C. § 112

A. 35 U.S.C. § 112, First Paragraph

Claims 13-30 were rejected as lacking enablement. The Examiner objected to various aspects of the claims as overbroad.

Claim 13 has been cancelled and new claim 31 has been added. Claim 31 is drawn to a method of determining relative age-related risk of colorectal cancer in a subject susceptible thereto comprising determining whether the alleles of the MnSOD gene in the subject comprise mutations which disrupt the α-helical structure of the mitochondrial targeting sequence (MTS) of the MnSOD protein, and assigning a relative risk of early onset colorectal cancer based on whether the subject has zero, one or two alleles comprising such a mutation. The subject can then be subjected to prophylactic treatments (e.g., changes in diet, increase in antioxidant intake), as well as implementation of age-appropriate diagnostic methods based on the subject's relative risk, as described in the specification.

Claim 31, like the claims granted by the PTO in the St. Clair reference cited by the Examiner, is tied to mutations in a discrete domain of the MnSOD gene which affect a necessary function, that of mitochondrial import. A working example of this method is given in the specification. Both the range of ages of colorectal cancer onset and the median age of onset exhibit a clear effect of a mutation in the MTS leading to a relatively high risk of earlier onset in subjects having both alleles so mutated, and an intermediate risk of earlier onset in subjects having one allele so mutated, with patients having no such mutations having exhibiting a low risk of early onset. *See* Figure 2 in particular, demonstrating the range of onset and median onset of colorectal cancer in subjects having 0, 1 or 2 wild type (versus mutated) alleles of MnSOD.

Mitochondrial targeting sequences have been well characterized in the art. They rely on an amphipathic helix containing charged residues on one face of the helix and hydrophobic residues on the other for insertion into the mitochondrial membrane, leading to

import of the protein into the mitochondrion.

MnSOD, which functions in the mitochondrion to catalytically remove damaging superoxide ions, relies on a MTS for import into the mitochondrion. Applicants have demonstrated that a mutation that disrupts the MTS of MnSOD, inhibiting its import into the mitochondrion, leads to a dose dependent effect on the relative risk of early onset colorectal cancer.

The relationship between the mutation and the deleterious effect is not complicated. MnSOD is directly responsible for removing a damaging species from a critical organelle of the cell. Mutations in a discrete domain of MnSOD directly necessary for its function impair its function. The deleterious effects of a mutation in MnSOD thus can directly result in cell damage. This mechanism thus does not rely on multiple "hits" in signaling pathways having multiple proteins in order to result in cell damage; the effect can be directly understood from the catalytic activity of the protein. The direct nature of this relationship is evidenced by the mutation dosage effect shown in the present invention. The invention as claimed therefore ties mutations directly affecting the function of a protective protein to earlier onset of a particular disease, as disclosed in the specification.

Furthermore, Applicants chose to perform their study in Hispanics, an underserved population whose involvement in medical studies should be encouraged, not used to impair Applicants' patent rights. The Examiner has provided no evidence that the mitochondria of Hispanic persons function differently than those of other groups, that mitochondrial import (a conserved mechanism among eukaryotes) is somehow different in Hispanics, or that Hispanics have different levels of superoxide in their mitochondria. Given the straightforward nature of the relationship between mutations affecting the function of the protein and increased cellular damage by the superoxide radical, there is no plausible scientific evidence to support any assertion that Hispanics differ from other groups in this conserved function. Any group of subjects having one or more mutations disrupting the α-helical structure of the MTS of MnSOD would be expected to have decreased levels of MnSOD in the mitochondrion, leading to increased risk of cell damage. As Applicants have shown that this mechanism leads to an age-related relative risk of early onset colorectal cancer, there is now scientific support for such mutations having similar effects in all subjects. No scientific evidence has been cited to the contrary.

The amended claims are therefore asserted to be fully enabled for their scope. The Examiner is therefore respectfully requested to withdraw the rejections under 35 U.S.C. § 112, first paragraph.

B. **35 U.S.C. § 112, Second Paragraph**

Claims 13-30 were rejected as indefinite on various grounds, including lacking a final process step. New claim 31, from which all the pending claims under consideration now ultimately depend, recites a complete process. Claim 13 has been deleted. The additional terms or phrases to which the Examiner objected in claims 14, 15 and 24-30 have been deleted or amended to address the Examiner's concerns. The Examiner is therefore respectfully requested to withdraw the rejections under 35 U.S.C. § 112, second paragraph.

II. Rejections over St. Clair

Claims 13, 15, 16, 21 and 22 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Pat. No. 6,265,172 to St. Clair et al. ("St. Clair"). Claims 17-20 and 23 were rejected under 35 U.S.C. 103(a) as obvious over St. Clair in view of Cotton (Advances in Genome Biology (1991) Vol. 1, pages 253-300). The Examiner stated that St Clair teaches a polymorphism in the promoter region of the MnSOD gene which is associated with decreased MnSOD activity, and describes certain techniques for detecting that polymorphism. The Examiner relied on Cotton for additional techniques for detecting the polymorphism. No art rejections were provided against claims 24-30.

New claim 31, upon which all the claims under consideration ultimately depend, is drawn to a method of determining relative age-related risk of developing early onset colorectal cancer comprising determining whether each allele "of a manganese superoxide dismutase (MnSOD) gene in the subject comprises a mutation in the coding region for the mitochondrial targeting sequence (MTS) of the MnSOD protein resulting in a loss of α-helical structure in the MTS." Nothing in St. Clair or Cotton teaches or suggests analyzing the alleles of the MnSOD gene of a subject to determine whether mutations in the MTS are present that disrupt its α-helical structure, much less assigning a relative risk of developing early onset colorectal cancer on the basis of whether zero, one or two such mutations are present. As noted by the Examiner, St. Clair relates to mutations in the promoter region of MnSOD, and Cotton relates simply to generic

techniques for detecting single base changes in nucleic acid.

As the cited references neither teach nor suggest all the claim limitations, those references can neither anticipate nor render obvious the claimed invention. The Examiner is respectfully requested to withdraw the rejections under 35 U.S.C. 102(e) and 103(a).

CONCLUSION

Applicants respectfully request reconsideration of the claims in view of the above amendments and remarks. A notice of allowance is earnestly solicited. If a telephone conference would expedite allowance of this matter, the Examiner is welcome to contact the undersigned at (650) 849-4908.

If an appropriate payment does not accompany or precede this submission, the Commissioner is hereby authorized to charge any fees required under 37 C.F.R. §§ 1.16 and 1.17, including any petition for extension of time, or to credit any overpayment, to Deposit Account No. 501189, docket number 13761-7001.

NOTICE OF FIRM NAME CHANGE

Agent for Applicant wishes to inform the Office that the name of its firm has been changed to Bingham McCutchen LLP.

DATE: September 16, 2002

Respectfully submitted,

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